

Schizophrenia: Breakdown in the Well-regulated Lifelong Process of Brain Development and Maturation

George Bartzokis, M.D.

Recent evidence suggests that the temporal extent of brain development/maturation can be expanded into middle age when maximal white matter volume and myelination are reached in frontal lobes and association areas. This temporally expanded view of brain development underlies a more comprehensive conceptual model of schizophrenia that incorporates both the reduction of gray matter volume and the complementary expansion of white matter volume occurring from adolescence until middle age. The model posits that the brain is in a constant state of well-regulated structural and functional change roughly defined as periods of development continuing into middle age followed by degeneration. Multiple genetic and environmental factors can interfere with the

developmental processes resulting in a dysregulation of the complementary changes occurring in gray and white matter. This dysregulation in development results in an insufficient capacity to maintain temporal synchrony of widely distributed neural networks and is manifested in the heterogeneity of symptoms and cognitive impairments of schizophrenia. The model highlights the contributory role of myelination to synchronous brain function, provides explanations for inconsistencies in the existing literature, and suggests testable hypotheses and novel approaches for intervention efforts.
[*Neuropsychopharmacology* 27:672–683, 2002]
© 2002 American College of Neuropsychopharmacology.
Published by Elsevier Science Inc.

KEY WORDS: *Schizophrenia; Brain; Development; Myelin; White matter; Connectivity; Neural networks; Frontal; Temporal; Association regions*

Progress in understanding schizophrenia has been impeded by the lack of clear postmortem changes to suggest the mechanism causing the disease. In addition, objective markers of the disorder (analogous to the plaques and tangles of Alzheimer's disease) for con-

firming the "correct" diagnosis of the disease have yet to be identified (Harrison 1999; Andreasen et al. 1999). Nevertheless, recent histopathologic and neuroimaging techniques have demonstrated subtle structural changes that provide clues to the disorder's pathophysiology and heterogeneity despite the failure to identify a single pathophysiologic "lesion" (Harrison 1999). Brain imaging studies of adult patients have consistently documented enlarged cerebral spinal fluid (CSF) volumes (sulcal and ventricular), as well as subtle decreases in total brain volume and smaller gray matter volumes in a variety of locations (cortical, medial temporal lobe structures, and thalamus) (for reviews see Lawrie and Abukmeil 1998; Nelson et al. 1998; Pearlson and Marsh 1999; McCarley et al. 1999; Wright et al. 2000).

The search for the underlying pathophysiology of schizophrenia continues (Harrison 1999). A primary early hypothesis has been the possibility of "neuro-

From the Department of Neurology, University of California, Los Angeles, CA, Central Arkansas Veterans Healthcare System, Little Rock, AR, and Greater Los Angeles VA Healthcare System, West Los Angeles, CA.

Address correspondence to: George Bartzokis, M.D., 710 Westwood Plaza, Room 2-238, Los Angeles, CA 90095-1769. Tel.: (310) 206-3207; Fax: (310) 268-3266; E-mail: gbar@ucla.edu.

Received August 3, 2001; revised February 19, 2002; accepted April 26, 2002.

Online publication: 5/1/02 at www.acnp.org/citations/Npp050102297.

degeneration." Some investigators have argued that indicators of neuro-integrity show worsening over time beyond that associated with normal aging (see DeLisi et al. 1997). Considerable evidence indirectly supports a progressive loss of brain tissue volume occurring at some point during postnatal development. This evidence includes the larger extracerebral CSF volume with normal skull size in schizophrenia (as reviewed by Woods 1998), as well as postmortem evidence of decreased neuropil (as opposed to neurons themselves) in prefrontal, dorsolateral prefrontal, and occipital cortices (Selemon and Goldman-Rakic 1999; Uranova et al. 2001; Cotter et al. 2002). Longitudinal imaging studies comparing schizophrenic and control subjects age 10 or older have generally supported this hypothesis. Some of these studies have reported no progression of these atrophic brain changes (Degreef et al. 1992; DeLisi et al. 1992; Illowsky et al. 1988), but most report either progression limited to subgroups (Gur et al. 1998; Keshavan et al. 1998; Davis et al. 1998; Lieberman et al. 2001) or clear evidence of progressive atrophic changes (DeLisi et al. 1997; Giedd et al. 1999a; Rapoport et al. 1999; Baare et al. 2001; Mathalon et al. 2001).

Contradicting such evidence has been the absence of gliosis, the hallmark of neuro-degenerative processes involving cell loss that is not apoptotic. The absence of gliosis has been interpreted to suggest that schizophrenia is a neurodevelopmental rather than a neurodegenerative disorder (Weinberger 1987; Weinberger and Lipska 1995). The definition of neurodevelopment has been recently expanded and refined as brain development and maturation that occurs as a consequence of an orderly process which begins in utero and continues into the early twenties (Woods 1998).

In this article, the neurodegenerative and the neurodevelopmental models are integrated with recent evidence that the temporal domain of brain development/maturation extends into middle age (Bartzokis et al. 2001). In the context of continuing myelination and expansion of white matter volume in normal individuals, these two hypotheses are clearly not exclusive of each other. The evidence for "neurodegeneration without gliosis" can be reinterpreted as an arrest in the developmental process of myelination (Bartzokis et al. 2001). This integrated view provides hypothetical explanations for multiple aspects of the observed phenomenology of the disease which, given the currently available research techniques, are amenable to hypothesis-driven prospective investigation.

EXTENDING THE TEMPORAL DOMAIN OF BRAIN DEVELOPMENT

Magnetic resonance imaging (MRI) can investigate myelination in vivo through the use of T1-weighted and

inversion-recovery sequences, which maximize brain gray/white matter contrast (Valk and van der Knaap 1989; Bartzokis et al. 1993). Using this method it has recently been demonstrated in vivo that the frontal and temporal lobe white matter volumes of normal males continue to increase into the mid-to-late forties, reaching maximum volume at age 47 (Bartzokis et al. 2001). These results are consistent with post mortem data showing that white matter myelination of these same regions continues into middle age (Yakovlev and Lecours 1967; Benes et al. 1994).

The gray matter changes accompanying postnatal brain development are equally marked, have the same quadratic shape as the white matter changes, but occur three decades before the white matter changes (Giedd et al. 1999a; Bartzokis et al. 2001). Early postnatal mammalian brain development is characterized by synaptogenic overelaboration of neuritic processes (i.e., axons and dendrites) in the cortex followed by a gradual reduction of synaptic density to about 60% of maximum levels (Huttenlocher 1979; Huttenlocher and Dabholkar 1997). Early in development, synaptogenesis likely creates connections more or less randomly, with subsequent selective elimination of weaker connections based on experience (Murphy and Regan 1998) as well as endogenous factors (Etienne and Baudry 1990; Bock and Braun 1999; Sestan et al. 1999). In humans this process is largely complete by the age of two years in sensory areas such as the occipital cortex, but is not complete until mid-adolescence in prefrontal and association (temporal and parietal) areas (Huttenlocher 1979; Giedd et al. 1999a).

Imaging studies of normal development have demonstrated that after early adolescence, when maximum total gray matter volume is reached (Giedd et al. 1999a), cortical gray matter volume continues to decrease throughout the life-span (Jernigan et al. 1991; Lim et al. 1992; Pfefferbaum et al. 1994; Sullivan et al. 1995; Raz et al. 1997; Passe et al. 1997; Gur et al. 1999; Bartzokis et al. 2001). Post-mortem data suggests that this gray matter volume decrease is primarily a result of large neuron shrinkage and pruning of processes with minimal if any neuronal cell loss before the age of 55 (Terry et al. 1987; Haug 1987; Pakkenberg and Gundersen 1997; Peters et al. 1998).

Thus, during normal post-adolescent development and maturation of the prefrontal and association areas, the gray matter volume reduction occurs in concert with an expansion in white matter volume that continues into middle age (Yakovlev and Lecours 1967; Benes et al. 1994; Bartzokis et al. 2001). These two opposing processes are well regulated and volumetrically cancel each other out creating the appearance, when the entire brain volume is measured, that in normal individuals, minimal if any changes in brain volume occur during adulthood (20–50 years of age) (Miller et al. 1980; Bart-

zokis et al. 2001). The gray/white matter ratio is significantly negatively correlated with age in this age range (Miller et al. 1980; Bartzokis et al. 2001, 2002b). However, the myelination-driven white matter volume expansion of frontal and temporal lobe regions (Yakovlev and Lecours 1967; Benes et al. 1994; Bartzokis et al. 2001) may be crucial for normal adult brain function (Benes et al. 1994; Fuster 1999). If normal white matter myelination/maturation is disrupted even in adulthood, normal adult brain function may become impaired (Bartzokis et al. 2001, 2002b).

MYELINATION AND BRAIN FUNCTIONAL SYNCHRONY

Multiple investigators have recently highlighted the importance of temporal synchrony of functional neural networks (for review see Miller 2000). A rich nomenclature has evolved around the general concept of functional synchrony of neural networks in schizophrenia. An inadequate amount of functional synchrony has been described from a variety of points of view as “disconnection syndrome,” “reduced neuropil,” “dysmetria,” and “cortical oscillations” (Friston and Frith 1995; Friston 1998; Weinberger and Lipska 1995; Selemon and Goldman-Rakic 1999; Andreasen et al. 1999; Fuster 1999; Green 1999).

White matter myelination may play a crucial role in supporting the brain's functional synchrony. Adequate speed of neural transmission may be especially important in the prefrontal cortex. The prefrontal cortex is the most highly interconnected of all the neocortical regions. It has reciprocal connections with the brainstem, hypothalamus, limbic system, thalamus, and other areas of the neocortex (for review see Miller 2000). One of the basic neurocognitive functions subserved by the prefrontal cortex is the temporal organization that is essential to the formation of associations between disparate events separated in time or “gestalts” in the temporal domain (Fuster 1999; Levy and Goldman-Rakic 2000; Miller 2000).

The speed of neural transmission depends on the structural properties of the connecting fibers, including axon diameter and the thickness of the insulating myelin sheath (Aboitiz et al. 1992). By increasing transmission speed, an increase in myelination could improve the connectivity of the brain and facilitate the synchronous integration of information across the many spatially segregated associative neocortical regions involved in higher cognitive functions (Gould et al. 1999; Srinivasan 1999; Mesulam 2000; Thompson et al. 2000).

If an analogy with today's internet were to be made, brain development and maturation in the association regions seems to consist of a progressive conversion of the internet from a telephone line-based transmission system to the faster T1 line-based system. The increase in transmission speed would permit a smooth transi-

tion from local institutional networks (local neuronal circuits) to the preeminence of the “virtual” institution existing in multiple geographic locations, but containing the necessary or even expanded levels of expertise and functional capacity (e.g., functional neural networks) (Bartzokis et al. 2001).

The literature has multiple reports of lower white matter volumes in schizophrenia compared with matched normal controls (Breier et al. 1992; Buchanan et al. 1998; Cannon et al. 1998; Sanfilippo et al. 2000; Bartzokis et al. 2001). Technical factors may make such observations less likely in the usual axial analysis of the brain used in imaging studies if the differences are localized to frontal and association regions (Bartzokis et al. 2001), the only areas where post mortem data indicates that myelination continues into adulthood (Yakovlev and Lecours 1967). An abnormality in the normal white matter volume expansion is also indirectly suggested by multiple other imaging and post mortem findings.

Recent studies using diffusion anisotropy (a MRI measure used to evaluate the structural integrity of white matter tracts) have consistently found abnormal values in schizophrenia (Buchsbaum et al. 1998; Lim et al. 1999; Foong et al. 2000). Although not as consistent (Bartha et al. 1999), two proton magnetic resonance spectroscopy studies also observed white matter abnormalities (Maier and Ron 1996; Lim et al. 1998), including age-related choline abnormalities suggestive of abnormal (reduced) myelination in the temporal lobe of schizophrenic patients (Maier and Ron 1996). These findings are consistent with recent evidence that in addition to neurons, mature oligodendrocytes also produce N-acetyl aspartate (NAA) (Bhakoo and Pearce 2000) and may contribute to the NAA signal observed in proton spectroscopy studies (Lim et al. 1998). In addition, the post-mortem literature may be consistent in reports of increased density of interstitial cells in white matter (Akbarian et al. 1996; Kirkpatrick et al. 1999). This finding could be reinterpreted in the context of the model to suggest that the reduced white matter volume in schizophrenia causes the increased density as opposed to an altered production of these cells. Interestingly, all the above investigations reporting white matter abnormalities in schizophrenia examined primarily older (mean age 34 or greater) samples of schizophrenic patients. In such older/chronic samples, an arrest in white matter development could be magnified when contrasted to the continued white matter myelination occurring in normal controls (Bartzokis et al. 2001) producing a highly significant Age X Diagnosis interaction ($p = .0002$) (Bartzokis et al. 2002b). Finally, two in vivo phosphorus magnetic resonance spectroscopy studies of drug-naïve schizophrenic subjects observed changes consistent with increased membrane breakdown, suggesting that a destructive white matter process may be already present at disease onset (Pettegrew et al. 1991;

Fukuzako et al. 1999). In support of the above studies, a recent post mortem study observed that several genes expressed in oligodendrocytes and involved in myelination were transcriptionally downregulated in schizophrenia (Hakak et al. 2001).

Subtle cortical gray matter volume decrements have also been observed by numerous investigators evaluating the pathophysiology of schizophrenia (for reviews see Lawrie and Abukmeil 1998; Nelson et al. 1998; Pearlson and Marsh 1999; McCarley et al. 1999; Wright et al. 2000). Compared with normal controls, individuals with schizophrenia seem to undergo an exaggerated reduction of gray matter volume in the context of minimal neuronal loss (Selemon and Goldman-Rakic 1999; McGlashan and Hoffman 2000; Woods 1998). The gray matter volume deficits observed in schizophrenia appear to be already present at the onset of the disease and to be non-progressive (Gur et al. 2000a,b; for review see Pearlson and Marsh 1999). Interestingly however, prospective studies in adults with schizophrenia find CSF volume expansions to be more robust and consistently observed than the accelerated (compared with controls) gray matter reductions (Lieberman et al. 2001; Mathalon et al. 2001; for review see Wright et al. 2000). Given that in adults the volume of the cranial vault is static, this would suggest that a lack of white matter expansion in schizophrenic compared with control subjects could contribute to the consistency and magnitude of CSF volume expansions observed in schizophrenia (Symonds et al. 1999; Bartzokis et al. 2002b).

Some recent studies observe that relatives of schizophrenic patients have gray matter volume reductions similar to the schizophrenic probands (Cannon et al. 1998; Baare et al. 2001) but white matter volume reductions are not found in these non-symptomatic relatives (Cannon et al. 1998). It is therefore possible that gray matter volume reductions represent genetically loaded deficits (Cannon et al. 1998; Seidman et al. 1999; Staal et al. 2000; Gur et al. 2000a,b; Baare et al. 2001). These gray matter deficits could be due to an early underdevelopment of synaptic connectivity (which may result in smaller heads) or overaggressive pruning process occurring primarily in the pre-adolescence period which may result in normal head size but smaller brain volume at illness onset (McGlashan and Hoffman 2000; Woods 1998; Giedd et al. 1999b; Rapoport et al. 1999).

Since reduced gray matter volumes are seen in normal relatives of schizophrenic patients (Cannon et al. 1998; Baare et al. 2001), inadequate myelination (whether due to lack of normal development or myelin breakdown) could represent secondary deficits necessary to produce enough brain functional synchrony impairment to fully manifest schizophrenic symptoms (Hyde et al. 1992). This possibility is supported by the observation that in discordant twin pairs the affected twin has enlarged lateral ventricles (Baare et al. 2001;

Ohara et al. 1998) which are closely associated with cerebral white matter volume (Symonds et al. 1999; Bartzokis et al., unpublished observation). Abnormal white matter development would impair the overall ability of the brain to maintain functional synchrony and, in concert with the continuous decreases in gray matter volumes which occur after early adolescence, result in an irreversible deterioration from previous levels of functioning (Woods 1998; Bartzokis et al. 2001). Compared with normal controls, the lack of compensating myelination in the face of the continued normal life-long reductions in gray matter volumes (Bartzokis et al. 2001) could contribute to progression of symptoms after illness onset and the appearance of continued brain "degenerative" changes in the absence of gliosis (DeLisi 1997).

WHITE MATTER DISEASE AND PSYCHOTIC SYMPTOMS

Despite the apparent importance of the prefrontal cortex and associative regions in schizophrenia, no cortical injury to these regions has been known to result in a schizophrenic syndrome (Weinberger and Lipska 1995; Fuster 1999). On the other hand, multiple white matter pathologies such as metachromatic leukodystrophy, 22q11 deletion syndrome (22qDS), and demyelinating disorders have been reported to result in chronic schizophrenic syndromes in adolescence and adulthood (Hyde et al. 1992; Bassett and Chow 1999) and possibly also in old age (Tonkonogy and Geller 1999; Sachdev et al. 1999). These white matter pathologies may be more prone to cause chronic psychoses if they are widespread, have an insidious onset, and most importantly, if they impair brain functional synchrony as opposed to completely obliterating the connectivity as occurs in lobotomies (Hyde et al. 1992). In addition, as Hyde and colleagues (1992) suggested, the white matter deficit itself may not be sufficient, as metachromatic leukodystrophy-associated psychosis is not manifested at younger ages. One could posit that at younger ages, before a critical amount of gray matter pruning has occurred, the local processing capacity created by the abundant local neuronal connectivity of the brain's association areas serves as a protective factor until additional pruning occurs in late childhood and adolescence phase (Huttenlocher 1979; Giedd et al. 1999a).

The postulated impairment of the brain's functional synchrony created by white matter diseases such as the ones described above could also be insidiously produced by dysregulation or arrest of the normal myelination of the frontal and association areas (Yakovlev and Lecours 1967; Benes et al. 1994; Bartzokis et al. 2001, 2002b). In such a circumstance, the cortical gray matter pruning of local neuronal connectivity would not be appropriately compensated by the increased connectivity provided by myelination of the appropri-

ate neural networks and could thus result in a brain dysfunction manifested as symptoms of schizophrenia.

The most recent evidence of the possible involvement of white matter pathology in chronic psychotic symptom production has come from studies of chromosome 22q11-deletion syndrome (22qDS), which until the recent discovery of its genetic basis, was often indistinguishable from and considered to be "schizophrenia." 22qDS encompasses several genetic syndromes associated with chromosome 22q 11.2 microdeletions, including velocardiofacial syndrome and DiGeorge syndrome (for review see Bassett and Chow 1999). It is the second most common genetic syndrome after Down syndrome with an estimated prevalence of the deletion of 1/4000 (Du Montcel et al. 1996), and it usually occurs as a sporadic mutation, but approximately 10% of cases are inherited from less severely affected parents (Demczuk and Aurias 1995). In addition to learning disabilities, palatal and cardiac abnormalities, and typical facial features, this syndrome is characterized by an unusual prevalence of psychotic symptoms (for review see Chow et al. 1999). Early studies summarized by Bassett and Chow (1999) indicate that for a patient with 22qDS the risk of schizophrenia may be approximately 25 times the general population risk, and double the risk for a first-degree relative of an individual with schizophrenia.

Unlike metachromatic leukodystrophy, which is known to be a myelin disease, the pathophysiology of 22qDS disorders remains unclear. However, early reports show the prevalence of white matter abnormalities in the 22qDS population to be very high. Eliez et al. (2000, 2001) studied children and adolescents and matched normal controls and observed that the 22qDS schizophrenic subjects had reductions in white matter volume twice as large as their gray matter volume reductions, a finding already independently replicated by two other groups (Kates et al. 2001; Bearden et al. 2001). In addition, Chow et al. (1999) observed that in a sample of 11 adults with 22qDS schizophrenia the most prevalent qualitative abnormality detected on MRI was T2 white matter bright foci which occurred with a frequency of 90% (in all but one of the subjects) and which are often a result of a demyelinating processes (Takao et al. 1999). In addition, a recent study supports the association between this genetic defect, schizophrenia, and lipid metabolism by demonstrating that apolipoprotein L, an enzyme involved in cholesterol transport, is upregulated in the brain of schizophrenic patients, as well as being located in the same 22q region involved in q22DS (Mimmack et al. 2002).

STRESS AND BRAIN TOXICITY

One of the most difficult to explain facets of schizophrenia (as well as other psychiatric diagnoses) is symptom exacerbation, which occur even in the face of continual

treatment. This is coupled with the observation that schizophrenia is an acutely "stress reactive" disease meaning that both the onset and the course of the disease are often associated with environmentally produced psychological stress (going to college, becoming homeless, etc.). Thus the *Vulnerability/stress model of schizophrenic episodes* (Nuechterlein et al. 1986) was developed to deal with the fact that environmental stressors may precipitate psychotic periods in vulnerable individuals.

One of the possible mechanisms for such a vulnerability/stress interaction is the neuronal and/or glial cell loss secondary to hypercortisolemia, which increases vulnerability to excitatory amino acid toxicity and may be manifested as a decrease in hippocampal volume (Sheline 1996; for review see Sapolsky 2000). This mechanism also interferes with adult neurogenesis (Sapolsky 2000) and could represent additional disruptions that contribute to impairing the functional synchrony of neural networks. Oligodendrocytes are also highly vulnerable to excitotoxicity (McDonald et al. 1998; Alonso 2000). Thus both gray and white matter structures may be vulnerable to stress, suggesting that there could be multiple ways to arrive at symptomatic exacerbations through further disruption of the already compromised ability of the vulnerable schizophrenic brain to maintain functional synchrony.

Such stress-dependent mechanisms have been associated with positive symptoms of schizophrenia (Walder et al. 2000) and may help explain reports that length of untreated illness may be associated with poorer outcome (Haas et al. 1998; for review see McGlashan 1999; Friedman et al. 1999). Conversely, some data suggest that early intervention with antipsychotic medications decreases some of the long-term morbidity associated with schizophrenia (Wyatt and Henter 1998). Since the effects of severe positive symptoms on outcome are present in both first admission and chronic schizophrenic patients with multiple previous hospitalizations (Haas et al. 1998), it is possible that any deleterious effects of severe positive symptoms may continue to exert an effect on outcome later in the illness. One longitudinal study suggests that geriatric patients that demonstrated cognitive and functional decline during a 30-month period had more severe positive symptoms at baseline (Harvey et al. 1999). Interventions that mitigate the physiologic effects of such stresses could provide novel avenues of treating these disorders by "protecting" normal brain developmental processes.

THERAPEUTIC INTERVENTIONS TO IMPROVE MYELINATION

If as hypothesized in the current model decreased myelination promotes loss of brain functional synchrony

and subsequent increased risk of psychotic symptoms, then increased myelination may offer protection from the same. Myelination differences could therefore help explain the well described gender effect in schizophrenia. In the first three decades of life normal females have a significantly greater amount of myelin staining in temporal lobe white matter tracks than male subjects of the same ages (Benes et al. 1994). In individuals at risk for schizophrenia, degree of myelination may be a protective factor for the appearance of symptoms. This protective factor may be underlying the well-described delay in onset of schizophrenia for females and their more benign course of disease (Castle et al. 1998; Hafner et al. 1998; Takahashi et al. 2000; Welham et al. 2000). Conversely, slower myelination in males compared with females could contribute to their vulnerability in acquiring earlier-onset schizophrenia (Benes et al. 1994; Koenig et al. 2000; Chance et al. 1999).

Steroids are one of the factors known to influence myelination (Melcangi et al. 1998; Desarnaud et al. 1998). The brain is capable of producing neurosteroids (steroid hormones produced locally in the brain) (for review see Baulieu and Schumacher 2000). Receptors for sex steroids such as estradiol and progesterone are present in both neurons and glia, and production of these neurosteroids occurs in glia including myelinating glial cells such as oligodendrocytes (Zwain and Yen 1999). One neurosteroid (progesterone) is known to stimulate myelination (Melcangi et al. 1998; Desarnaud et al. 1998). The availability of progesterone from the periphery, as well as a higher level of the enzymes involved in neurosteroid synthesis in female brains (Watzka et al. 1999), may be two of the reasons for the earlier myelination observed in female brain (Benes et al. 1994; Chan et al. 1998). Since blood levels of female sex steroids such as progesterone are very low in males, the male nervous system may rely more heavily on local production of these hormones for myelination. Male brains could therefore be more susceptible to inhibitors of the enzymes (cytochrome P450 side chain cleavage enzyme and 3β -hydroxysteroid dehydrogenase) involved in the synthesis of neurosteroids (Baulieu and Schumacher 2000). Thus, deficits in myelination whether due to steroid availability or other causes could contribute to the gender specific pathophysiology of schizophrenia. The atypical antipsychotics clozapine and olanzapine, but not the typical antipsychotic haldol, have been shown to increase neurosteroid levels (including progesterone) in the cortex and striatum of rats (Barbaccia et al. 2001; Marx et al. 2000).

Abnormalities in lipid metabolism are another possible mechanism that could interfere with myelination in schizophrenia. This possibility is indirectly supported by a large literature describing abnormal lipid metabolism in psychiatric disorders (for review see Horrobin and Bennett 1999; Assies et al. 2001). In addition, apoli-

poprotein D (involved in lipid metabolism and shown to bind hydrophobic ligands including steroid hormones and arachidonic acid) is reduced in the plasma of schizophrenic subjects while being elevated in a regionally specific pattern in the brain of schizophrenic patients as well as bipolar patients who were psychotic prior to death (Thomas et al. 2001b).

Glia synthesize, excrete, and express the gene for apolipoprotein D, suggesting a specific role for this molecule in membrane lipid metabolism and repair in the central nervous system (CNS) (Schaeren-Wiemers et al. 1995; Kalman et al. 2000; Patel et al. 1995). Apolipoprotein D levels have been shown to be elevated in old age and in a number of other neuropathologic disorders such as Alzheimer's disease (Kalman et al. 2000) and excitotoxic damage (Montpied et al. 1999) in regionally specific patterns. This suggests that upregulation of apolipoprotein D may be a localized response to regional brain lipid pathology (for review see Rassart et al. 2000). This possibility is supported by the observation that in an animal model of Niemann-Pick disease (degenerative disease involving cholesterol homeostasis) most of the apolipoprotein D was associated with the myelin fraction (Suresh et al. 1998). In normal brain, apolipoprotein D is found primarily in white matter oligodendrocytes (Navarro et al. 1998; Ong et al. 1999). Finally, in normal younger adults who are continuing to myelinate (Yakovlev and Lecours 1967; Benes et al. 1994; Bartzokis et al. 2001), brain apolipoprotein D is primarily localized in oligodendrocytes (Schaeren-Wiemers et al. 1995; Navarro et al. 1998; Kalman et al. 2000) as is the case in the rodent CNS where a maturation-associated induction of the gene's expression has been reported (Ong et al. 1999).

Interestingly, some of the novel antipsychotic medications like clozapine but not classic neuroleptics like haldol seem to be able to markedly increase apolipoprotein D levels in brain (Thomas et al. 2001a,b; Khan et al. 2002) as well as cause elevated blood lipids in humans (Henderson et al. 2000; Melkersson et al. 2000). This suggests that in addition to neuronal receptor effects, novel antipsychotic medications may be capable of producing therapeutic effects by impacting abnormalities of lipid metabolism and myelination (Thomas et al. 2001a; Khan et al. 2002). Medications that impact lipid metabolism may prove effective in correcting white matter deficits in schizophrenia (Bartzokis et al. 2002b; Lieberman et al. 2001a). Additional indirect evidence for the association between effects on lipid metabolism and therapeutic response to antipsychotic medications comes from data suggesting that increasing body weight is associated with the robustness of clinical response (Basson et al. 2001).

Finally, novel pharmacologic agents that have been developed for their neuroprotective/neurotrophic properties have been shown have promyelination effects

(Demerens et al. 1999). In light of the proposed model of schizophrenia involving the arrest of normal myelination, the prospect of correcting myelination deficits or promoting myelination is promising. Such interventions open up the potential to go beyond ameliorative treatments and move the field toward curative treatments by impacting myelination, one of the possible underlying developmental abnormalities of the schizophrenic diseases (Bartzokis et al. 2002b).

Evidence from the study of groups of patients that experience deteriorating course and poor clinical outcomes suggests that this most severely affected and treatment resistant group may be especially likely to benefit from interventions that may improve myelination. This subgroup demonstrates severe negative symptoms and cognitive deterioration which seems to affect learning that occurred during the years of illness as opposed to skills such as reading acquired during formal education (Harvey et al. 1999, 2000; McGurk et al. 2000). This subgroup demonstrates myelin gene product downregulation (Hakak et al. 2001) as well as progressive enlargement of lateral ventricle spaces (Davis et al. 1998; Lieberman et al. 2001) in the absence of pathologic evidence of known dementing neurodegenerative disorders such as Alzheimer's disease (Purohit et al. 1998). Progressive enlargement of the lateral ventricles would be expected if the normal increase in white matter volume observed in adulthood did not occur (Bartzokis et al. 2001, 2002a,b, unpublished data). Thus, early intervention with promyelinating agents could have especially far reaching consequences on the course of illness in this subgroup by correcting the myelination "trajectory" of their brain development.

CONCLUSIONS

The accumulated evidence over the past few decades suggests that schizophrenia is a heterogeneous disorder lacking a single pathophysiologic "lesion." Recent evidence suggests that a temporally expanded view of brain development may be relevant to creating a better conceptual model aimed at understanding schizophrenia and possibly other neuropsychiatric disorders. This developmental model posits that the brain is in a constant state of change roughly defined as periods of development/maturation continuing into middle age followed by degeneration.

One of the underlying hypotheses is that the process of brain maturation is based on increasing synchrony of communication between disparate brain regions that encompass widely distributed neural networks. This increased synchrony is achieved in part by increasing speed of neural transmission through a process of myelination that continues into middle age and possibly beyond. For normal development to occur, this neu-

rodevelopmental white matter process must be regulated and occur in concert with the concurrent gray matter process that results in pruning of local neuronal interconnections and is manifested by a continually decreasing brain gray matter volume after adolescence. Genetic and/or environmental effects that interfere with either one or both of these two well regulated developmental processes may result in a loss of the brain's ability to function normally by reducing its ability to maintain synchronous communication across functional neural networks. This loss of synchrony can occur between a variety of such networks and therefore results in a heterogeneous group of devastating symptoms that we currently refer to as schizophrenia.

This model suggests that the brain could experience neurodevelopmental dysregulation at any point, if pathological states (e.g., genetic, hormonal, head trauma, severe stress (including psychological stress), substance abuse, etc.) alter the normal age-related pattern of continual structural and functional changes. This temporally expanded view of brain development creates the possibility of testing its underlying hypotheses through prospective imaging studies focused on areas of active myelination, combined with prospective evaluation of neurocognitive and symptomatic aspects of the disease, and genetic studies targeting proteins involved in myelination. The model would also predict that that medications or other interventions (hormonal, dietary) that protect myelin or normalize/enhance myelination could result in improvements.

ACKNOWLEDGMENTS

This work was supported by the Research and Psychiatry Services of the Department of Veterans Affairs, the National Alliance for Research on Schizophrenia and Depression, NIMH grant MH-51928, and the Marie Wilson Howells Endowment. The author thanks Po H. Lu for editorial support and Lori Altshuler, M.D., for reviewing the manuscript.

REFERENCES

- Aboitiz F, Scheibel AB, Fisher RS, Zaidel E (1992): Fiber composition of the human corpus callosum. *Brain Res* 598: 143–153
- Akbarian S, Kim JJ, Potkin SG, Hetrick WP, Bunney WE, Jones EG (1996): Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. *Arch Gen Psychiatry* 53:425–436
- Alonso G (2000): Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* 31:219–231
- Andreasen NC, Napoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M (1999): Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. *Biol Psychiatry* 46:908–920

- Assies J, Lieverse R, Vreken P, Wanders RJA, Dingemans PMJA, Linszen DH (2001): Significantly reduced docosahexaenoic and docosapentaenoic acid concentration in erythrocyte membranes from schizophrenic patients compared to matched control group. *Biol Psychiatry* 49:510–522
- Baare WFC, van Oel CJ, Hulshoff Pol HE, Schnack HG, Durston S, Sitskoorn MM, Kahn RS (2001): Volumes of brain structures in twins discordant for schizophrenia. *Arch Gen Psychiatry* 58:33–40
- Barbaccia ML, Affricano D, Purdy RH, Maciocco E, Spiga F, Biggio G (2001): Clozapine, but not haloperidol, increases brain concentrations of neuroactive steroids in the rat. *Neuropsychopharm* 25:489–497
- Bartha R, Al-Semaan YM, Williamson PC, Drost DJ, Malla AK, Carr TJ, Densmore M, Canaran G, Neufeld RWJ (1999): A short echo proton magnetic resonance spectroscopy study of the left mesial-temporal lobe in first-onset schizophrenic patients. *Biol Psychiatry* 45:1403–1411
- Bartzokis G, Beckson M, Lu PH, Edwards N, Bridge P, Mintz J (2002a): Brain maturation is arrested in chronic cocaine addicts. *Biol Psychiatry* 51:605–611
- Bartzokis G, Beckson M, Lu PH, Nuechterlein K, Edwards N, Mintz J (2001): Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Arch Gen Psychiatry* 58:461–465
- Bartzokis G, Mintz J, Marx P, Osborn D, Gutkind D, Chiang F, Phelan CK, Marder S (1993): Reliability of in vivo volume measures of hippocampus and other brain structures using MRI. *Magn Res Imaging* 11:993–1006
- Bartzokis G, Nuechterlein KH, Lu PH, Edwards N, Mintz J (2002b): Dysregulated brain development in adult men with schizophrenia: A magnetic resonance imaging study. (submitted)
- Bassett AS, Chow EW (1999): 22q11 deletion syndrome: a genetic subtype of schizophrenia. *Biol Psychiatry* 46:882–891
- Basson BR, Kinion BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD (2001): Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *J Clin Psychiatry* 62:231–238
- Baulieu EE, Schumacher M (2000): Progesterone as a neuroactive neurosteroid, with special reference to the effect of progesterone on myelination. *Steroids* 65:605–612
- Bearden CE, van Erp T, Glahn D, Wang PP, Monterosso JR, Zackai E, Emanuel B, Cannon TD (2001): Structural and functional neuroanatomy in the 22q deletion syndrome. *Biol Psychiatry* 49:195
- Benes FM, Turtle M, Khan Y, Farol P (1994): Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Arch Gen Psychiatry* 51:477–484
- Bhakoo KK, Pearce D (2000): In vitro expression of N-acetyl aspartate in oligodendrocytes: Implications for proton magnetic resonance spectroscopy signal in vivo. *J Neurochem* 74:254–262
- Bock J, Braun K (1999): Blockade of N-methyl-D-aspartate receptor activation suppresses learning-induced synaptic elimination. *Proc Natl Acad Sci USA* 96:2485–2490
- Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F (1992): Brain morphology and schizophrenia: A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Arch Gen Psychiatry* 49:921–926
- Buchanan RW, Vladar K, Barta PE, Pearlson GD (1998): Structural evaluation of the prefrontal cortex in schizophrenia. *Am J Psychiatry* 155:1049–1055
- Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, Downhill J, Haznedar M, Fallon JH, Atlas SW (1998): MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. *Neuroreport* 9:425–430
- Cannon TD, van Erp TG, Huttunen M, Lonnqvist J, Salonen O, Valanne L, Poutanen VP, Standertskjold-Nordenstam CG, Gur RE, Yan M (1998): Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. *Arch Gen Psychiatry* 55:1084–1091
- Castle D, Sham P, Murray R (1998): Differences in distribution of ages of onset in males and females with schizophrenia. *Schizophrenia Res* 33:179–183
- Chan JR, Phillips LJ, Glaser M (1998): Glucocorticoids and progesterins signal the initiation and enhance the rate of myelin formation. *Proc Natl Acad Sci USA* 95:10459–10464
- Chance SA, Highley JR, Esiri MM, Crow TJ (1999): Fiber content of the fornix in schizophrenia: lack of evidence for a primary limbic encephalopathy. *Am J Psychiatry* 156:1720–1724
- Chow EW, Mikulis DJ, Zipursky RB, Scutt LE, Weksberg R, Bassett AS (1999): Qualitative MRI findings in adults with 22q11 deletion syndrome and schizophrenia. *Biol Psychiatry* 46:1436–1442
- Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP (2002): Reduced neuronal size and glia cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cerebral Cortex* 12:386–394
- Davis KL, Buchsbaum MS, Shihabuddin L, Spiegel-Cohen J, Metzger M, Frecska E, Keefe RS, Powchik P (1998): Ventricular enlargement in poor-outcome schizophrenia. *Biol Psychiatry* 43:783–793
- Degreef G, Ashtari M, Bogerts B, Bilder RM, Jody DN, Alvir JM, Lieberman JA (1992): Volumes of ventricular system subdivisions measured from magnetic resonance images in first episode schizophrenic patients. *Arch Gen Psychiatry* 49:531–537
- Demerens C, Stankoff B, Zalc B, Lubetzki C Eliprodil (1999): Stimulates CNS myelination: new prospects for multiple sclerosis? *Neurology* 1999:346–350
- DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R (1997): Schizophrenia as a chronic brain process: A study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res: Neuroimaging* 74:129–140
- DeLisi LE, Striktzke P, Riordan H, Holan V, Boccio A, Kushner M, McClelland J, Van Eyl O, Anand A (1992): The timing of brain morphological changes in schizophrenia and their relationship to clinical outcome. *Biol Psychiatry* 31:241–254
- DeLisi LE (1997): Is schizophrenia a lifetime disorder of brain plasticity, growth and aging? *Schizophrenia Res* 23:119–129

- Demczuk S, Aurias A (1995): DiGeorge syndrome and related syndromes associated with 22q11.2 deletions: a review. *Ann Genet* 38:59–76
- Desarnaud F, Do Thi AN, Brown AM, Lemke G, Suter U, Baulieu EE, Schumacher M (1998): Progesterone stimulates the activity of the promoters of peripheral myelin protein-22 and protein zero genes in Schwann cells. *J Neurochem* 71:1765–1768
- Du Montcel ST, Mendizabal H, Ayme S, Levy A, Philip N (1996): Prevalence of 22q11 microdeletion. *J Med Genet* 33:719
- Eliez S, Antonarakis SE, Morris MA, Dahoun SP, Reiss AL (2001): Parental origin of the deletion 22q11.2 and brain development in velofacial syndrome. *Arch Gen Psychiatry* 58:64–68
- Eliez S, Schmitt JE, White CD, Reiss AL (2000): Children and adolescents with velocardiofacial syndrome: a volumetric MRI study. *Am J Psychiatry* 157:409–415
- Etienne P, Baudry M (1990): Role of excitatory amino acid neurotransmission in synaptic plasticity and pathology; an integrative hypothesis concerning the pathogenesis and evolutionary advantages of schizophrenia-related genes. *J Neural Transm* 29(suppl):39–48
- Foong J, Maier M, Barker GJ, Brocklehurst S, Miller DH, Ron MA (2000): In vivo investigation of white matter pathology in schizophrenia with magnetisation transfer imaging. *J Neurolog Neurosurg Psychiatry* 68:70–74
- Friedman JI, Harvey PD, Kamether E, Byne W, Davis KL (1999): Cognitive and functional changes with aging in schizophrenia. *Biol Psychiatry* 46:921–928
- Friston KJ (1998): The disconnection hypothesis. *Schizophr Res* 30:115–125
- Friston KJ, Frith CD (1995): Schizophrenia: a disconnection syndrome? *Clin Neurosci* 3:89–95
- Fukuzako H, Fukuzako T, Hashiguchi T, Kodama S, Takigawa M, Fujimoto T (1999): Changes in levels of phosphorus metabolites in temporal lobes of drug-naïve schizophrenic patients. *Am J Psychiatry* 156:1205–1208
- Fuster JM (1999): Synopsis of function and dysfunction of the frontal lobe. *Acta Psychiatrica Scandinavia* 99:51–57
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL (1999a): Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2:861–863
- Giedd JN, Jeffries NO, Blumenthal J, Castellanos FX, Vaituzis AC, Fernandez T, Hamburger SD, Liu H, Nelson J, Bedwell J, Tran L, Leane M, Nicolson R, Rapoport JL (1999b): Childhood-onset schizophrenia: progressive brain changes during adolescence. *Biol Psychiatry* 46:892–898
- Gould E, Reeves AJ, Graziano MSA, Gross CG (1999): Neurogenesis in the neocortex of adult primates. *Science* 286:548–552
- Green MF (1999): Cortical oscillations and schizophrenia. *Arch Gen Psychiatry* 56:1007–1008
- Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE (1999): Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J Neurosci* 19:4065–4072
- Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, Bilker WB, Gur RC (2000a): Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Arch Gen Psychiatry* 57:761–768
- Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, Gur RC (1998): Subcortical MRI volumes in neuroleptic-naïve and treated patients with schizophrenia. *Am J Psychiatry* 155:1711–1717
- Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, Arnold SE, Bilker WB, Gur RC (2000b): Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry* 57:769–775
- Haas GL, Garratt LS, Sweeney JA (1998): Delay to first antipsychotic medication in schizophrenia: impact on symptomatology and clinical course of illness. *J Psychiatr Res* 32:151–159
- Hafner H, Hambrecht M, Löffler W, Munk-Jorgensen P, Riecher-Rössler A (1998): Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. *Psychol Med* 28:351–365
- Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, Fienberg AA (2001): Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci USA* 98:4746–4751
- Harrison PJ (1999): The neuropathology of schizophrenia: A critical review of the data and their interpretation. *Brain* 122:593–624
- Harvey PD, Moriarty PJ, Friedman JI, White L, Parrella M, Mohs RC, Davis KL (2000): Differential preservation of cognitive functions in geriatric patients with lifelong chronic schizophrenia: less impairment in reading compared with other skill areas. *Biol Psychiatry* 47:962–968
- Harvey PD, Silverman JM, Mohs RC, Parrella M, White L, Powchik P, Davidson M, David KL (1999): Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. *Biol Psychiatry* 45:32–40
- Haug H (1987): Brain sizes, surfaces, and neuronal sizes of the cortex cerebri: a stereological investigation of man and his variability and a comparison with some mammals (primates, whales, marsupials, insectivores, and one elephant). *Am J Anat* 180:126–142
- Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC (2000): Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. *Am J Psychiatry* 157:975–981
- Horrobin DF, Bennett CN (1999): New gene targets related to schizophrenia and other psychiatric disorders: enzymes, binding proteins and transport proteins involved in phospholipid and fatty acid metabolism. *Prostaglandins Leukotrienes Essnt Fatty Acids* 60:141–167
- Huttenlocher PR, Dabholkar AS (1997): Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol* 387:167–178
- Huttenlocher PR (1979): Synaptic density in the human frontal cortex: developmental changes and effects of aging. *Brain Res* 163:195–205
- Hyde TM, Ziegler JC, Weinberger DR (1992): Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. *Arch Neurol* 49:401–406
- Illowsky BP, Juliano DM, Bigelow LB, Weinberger DR

- (1988): Stability of CT scan findings in schizophrenia: results of an 8 year follow-up study. *J Neurology Neurosurgery Psychiatry* 51:209–213
- Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR (1991): Cerebral structure on MRI, part I: localization of age-related changes. *Biol Psychiatry* 29:55–67
- Kalman J, McConathy W, Araoz C, Kasa P, Lacko AG (2000): Apolipoprotein D in the aging brain and in Alzheimer's dementia. *Neurol Res* 22:330–336
- Kates WR, Burnette CP, Jabs EW, Rutberg J, Murphy AM, Gardos MA, Geraghty M, Kaufmann WE, Pearlson GD (2001): Regional cortical white matter reductions in velocardiofacial syndrome: A volumetric MRI analysis. *Biol Psychiatry* 49:677–684
- Keshavan MS, Rosenberg D, Sweeney JA, Pettegrew JW (1998): Decreased caudate volume in neuroleptic-naïve psychotic patients. *Am J Psychiatry* 155:774–778
- Khan MM, Parikh VV, Mahadik SP (2002): Effects of chronic exposure of antipsychotics on apolipoprotein D in rat brain. *Biol Psychiatry* 51:168S
- Kirkpatrick B, Conley RC, Kakoyannis A, Reep RL, Roberts RC (1999): Interstitial cells of the white matter in the inferior parietal cortex in schizophrenia: An unbiased cell-counting study. *Synapse* 34:95–102
- Koenig HL, Gong WH, Pelissier P (2000): Role of progesterone in peripheral nerve repair. *Rev Reprod* 5:189–199
- Lawrie SM, Abukmeil SS (1998): Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies [see comments]. *Br J Psychiatry* 172:110–120
- Levy R, Goldman-Rakic PS (2000): Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res* 133:23–32
- Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, Bilder R (2001): Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry* 49:487–499
- Lieberman JA, Duncan G, Marx C, Grobin C, Morrow L (2001a): Atypical and Conventional Antipsychotic Drugs: Comparative Effects and Mechanism of Action. Abstracts of the 40th Annual Meeting of the ACNP, Hawaii, December 2001
- Lim KO, Adalsteinsson E, Spielman D, Sullivan EV, Rosenbloom MJ, Pfefferbaum A (1998): Proton magnetic resonance spectroscopic imaging of cortical gray and white matter in schizophrenia. *Arch Gen Psychiatry* 55: 346–352
- Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum A (1999): Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry* 56:367–374
- Lim KO, Zipursky RB, Watts MC, Pfefferbaum A (1992): Decreased gray matter in normal aging: An in vivo magnetic resonance study. *J Gerontol* 47:B26–30
- Maier M, Ron MA (1996): Hippocampal age-related changes in schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophrenia Res* 22:5–17
- Marx CE, Duncan GE, Gilmore JH, Lieberman JA, Morrow AL (2000): Olanzapine increases allopregnenalone in the rat cerebral cortex. *Biol Psychiatry* 47:1000–1004
- Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A (2001): Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 58:148–157
- McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, Shenton ME (1999): MRI anatomy of schizophrenia. *Biol Psychiatry* 45:1099–1119
- McDonald JW, Althomsons SP, Choi DW, Goldberg MP (1998): Oligodendrocytes from forebrain are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity. *Nat Med* 4:291–297
- McGlashan TH (1999): Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol Psychiatry* 46:899–907
- McGlashan TH, Hoffman RE (2000): Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry* 57:637–648
- McGurk SR, Moriarty PJ, Harvey PD, Parrella M, White L, Davis KL (2000): The longitudinal relationship of clinical symptoms, cognitive functioning, and adaptive life in geriatric schizophrenia. *Schizophrenia Res* 42: 47–55
- Melcangi RC, Magnaghi I, Cavarretta L, Martini L, Piva F (1998): Age-induced decrease of glycoprotein PO and myelin basic protein gene expression in the rat sciatic nerve. Repair by steroid derivatives. *Neuroscience* 85: 569–578
- Melkersson KI, Hulting AL, Brismar KE (2000): Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry* 61:742–749
- Mesulam M (2000): Principles of Behavioral and Cognitive Neurology, 2nd ed. New York, Oxford Univ Press
- Miller AK, Alston RL, Corsellis JA (1980): Variation with age in the volumes of grey and white matter in the cerebral hemisphere of man: measurements with an image analyser. *Neuropathol Appl Neurobiol* 6:119–132
- Miller EK (2000): The prefrontal cortex and cognitive control. *Nature Reviews Neuroscience* 1:59–65
- Mimmack ML, Ryan M, Baba H, Navarro-Ruiz J, Iritani S, Faull RLM, McKenna PJ, Jones PB, Arai H, Starkey M, Emson PC, Bahn S (2002): Gene expression analysis in schizophrenia: Reproducible up-regulation of several members of the apolipoprotein L family located in a high-susceptibility locus for schizophrenia on chromosome 22. *PANS* 99:4680–4685
- Montpied P, de Bock F, Lerner-Natoli M, Bockaert J, Rondouin G (1999): Hippocampal alterations of apolipoprotein E and D mRNA levels in vivo and in vitro following kainate excitotoxicity. *Epilepsy Res* 35:135–146
- Murphy KJ, Regan CM (1998): Contributions of cell adhesion molecules to altered synaptic weighting during memory consolidation. *Neurobiol Learn Mem* 70:73–81
- Navarro A, Tolivia J, Astudillo A, del Valle E (1998): Pattern of apolipoprotein D immunoreactivity in human brain. *Neurosci Lett* 254:17–20
- Nelson MD, Saykin AJ, Flashman LA, Riordan HJ (1998): Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. *Arch Gen Psychiatry* 55:433–440
- Nuechterlein KH, Dawson ME, Gitlin M, Vemtura J, Goldstein MJ, Snyder KS, Yee CM, Mintz J (1986): A heuristic

- vulnerability/stress model of schizophrenic episodes. *Schizophr Bull* 10:300–312
- Ohara K, Xu HD, Matsunaga T, Xu DS, Huang XQ, Gu GF, Ohara K, Wang ZC (1998): Cerebral ventricle-brain ratio in monozygotic twins discordant and concordant for schizophrenia. *Progress Neuro-Psychopharm Biol Psychiatry* 22:1043–1050
- Ong WY, Lau CP, Leong SK, Kumar U, Suresh S, Patel SC (1999): Apolipoprotein D gene expression in the rat brain and light and electron microscopic immunocytochemistry of apolipoprotein D expression in the cerebellum of neonatal, immature adult rats. *Neurosci* 1999; 90:913–22
- Pakkenberg B, Gundersen HJ (1997): Neocortical neuron number in humans: effect of sex and age. *J Comp Neurol* 384:312–320
- Passe TJ, Rajagopalan P, Tupler LA, Byrum CE, MacFall JR, Krishnan KRR (1997): Age and sex effects on brain morphology. *Prog Neuropsychopharmacol Biol Psychiatry* 21:1231–1237
- Patel SC, Asotra K, Patel YC, McConathy WJ, Patel RC, Suresh S (1995): Astrocytes synthesize and secrete the lipophilic ligand carrier apolipoprotein D. *Neuroreport* 6:653–6658
- Pearlson GD, Marsh L (1999): Structural brain imaging in schizophrenia: A selective review. *Biol Psychiatry* 46:627–649
- Peters A, Morrison JH, Rosene DL, Hyman BT (1998): Are neurons lost from the primate cerebral cortex during normal aging? *Cereb Cortex* 8:295–300
- Pettegrew JW, Keshavan MS, Panchalingam K, Strychor S, Kaplan DB, Tretta MG, Allen M (1991): Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naïve schizophrenics: a pilot study of the dorsal prefrontal cortex by in vivo phosphorus 31 nuclear magnetic resonance spectroscopy. *Arch Gen Psychiatry* 48:563–568
- Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994): A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol* 51:874–887
- Purohit DP, Perl DP, Haroutunian V, Powchik P, Davidson M, Davis KL (1998): Alzheimer disease and related neurodegenerative disease in elderly patients with schizophrenia. *Arch Gen Psychiatry* 55:205–211
- Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicholson R, Bedwell J, Leane M, Zijdenbos A, Paus T, Evans A (1999): Progressive cortical change during adolescence in childhood-onset schizophrenia: A longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 56:649–654
- Rassart E, Bedirian A, Do Carmo S, Guinard O, Sirois J, Terrisse L, Milne R (2000): Apolipoprotein D. *Biochim Biophys Acta* 1482:185–198
- Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, Loken WJ, Thornton AE, Acker JD (1997): Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb Cortex* 7:268–282
- Sachdev P, Brodaty H, Rose N, Cathcart S (1999): Schizophrenia with onset after age 50 years. 2: Neurological, neuropsychological and MRI investigation. *Br J Psychiatry* 175:416–421
- Sanfilippo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lantin A, Feiner D, Rotrosen J, Wolkin A (2000): Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. *Arch Gen Psychiatry* 57:471–480
- Sapolsky RM (2000): Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 57:925–935
- Schaeren-Wiemers N, Schaefer C, Valenzuela DM, Yancopoulos GD, Schwab ME (1995): Identification of new oligodendrocyte- and myelin-specific genes by a differential screening approach. *J Neurochem* 65:10–22
- Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Toomey R, Tourville J, Kennedy D, Makris N, Caviness VS, Tsuang MT (1999): Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. *Biol Psychiatry* 46:941–954
- Selemon LD, Goldman-Rakic PS (1999): The reduced neuro-pil hypothesis: A circuit based model of schizophrenia. *Biol Psychiatry* 45:17–25
- Sestan N, Arteranis-Tsakonas S, Rakic P (1999): Contact-dependent inhibition of cortical neurite growth mediated notch signaling. *Science* 286:741–746
- Sheline YI (1996): Hippocampal atrophy in major depression: a result of depression-induced neurotoxicity. *Mol Psychiatry* 1:298–299
- Srinivasan R (1999): Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. *Clin Neurophysiol* 110:1351–1362
- Staal WG, Hulshoff Pol HE, Schnack HG, Hoogendoorn ML, Jellema K, Kahn RS (2000): Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *Am J Psychiatry* 157:416–421
- Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A (1995): Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiol Aging* 16:591–606
- Suresh S, Yan Z, Patel RC, Patel YC, Patel SC (1998): Cellular cholesterol storage in the Niemann-Pick disease type C mouse is associated with increased expression and defective processing of apolipoprotein D. *J Neurochem* 70:242–251
- Symonds LL, Archibald SL, Grant I, Zisook S, Jernigan TL (1999): Does an increase in sulcal or ventricular fluid predict where brain tissue is lost? *J Neuroimaging* 9:201–209
- Takahashi S, Matsuura M, Tanabe E, Yara K, Nonaka K, Fukura Y, Kikuchi M, Kojima T (2000): Age at onset of schizophrenia: gender differences and influence of temporal socioeconomic change. *Psychiatry Clin Neurosci* 54:153–156
- Takao M, Koto A, Tanahashi N, Fukuuchi Y, Takagi M, Morinaga S (1999): Pathologic findings of silent hyperintense white matter lesions on MRI. *J Neurol Sci* 167:127–131
- Terry RD, DeTeresa R, Hansen LA (1987): Neocortical cell counts in normal human adult aging. *Ann Neurol* 21:530–539

- Thomas EA, Danielson PE, Nelson PA, Pribyl TM, Hilbush BS, Hasel KW, Sutcliffe JG (2001a): Clozapine increases apolipoprotein D expression in rodent brain: towards a mechanism for neuroleptic pharmacotherapy. *J Neurochem* 76:789–796
- Thomas EA, Dean B, Pavey G, Sutcliffe JG (2001b): Increased CNS levels of apolipoprotein D in schizophrenic and bipolar subjects: Implications for the pathophysiology of psychiatric disorders. *PANS* 98:4066–4071
- Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW (2000): Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature* 404:190–193
- Tonkonogy JM, Geller JL (1999): Late-onset paranoid psychosis as a distinct clinicopathologic entity: magnetic resonance imaging data in elderly patients with paranoid psychosis of late onset and schizophrenia of early onset. *Neuropsychiatry Neuropsychol Behav Neurol* 12:230–235
- Uranova N, Orlovskaya D, Vikhрева O, Zimina L, et al. (2001): Electron microscopy of oligodendroglia in severe mental illness. *Brain Res Bull* 55:597–610
- Valk J, van der Knaap MS (1989): *Magnetic Resonance of Myelin, Myelination, and Myelin Disorders*. New York, Springer-Verlag
- Walder DJ, Walker EF, Lewine RJ (2000): Cognitive functioning, cortisol release, and symptom severity in patients with schizophrenia. *Biol Psychiatry* 48:1121–1132
- Watzka M, Bidlingmaier F, Schramm J, Klingmuller D, Stofel-Wagner B (1999): Sex- and age-specific differences in human brain CYP11A1 mRNA expression. *J Neuroendocrinol* 11:901–905
- Weinberger DR, Lipska BK (1995): Cortical maldevelopment, anti-psychotic drugs, and schizophrenia: a search for common ground. *Schizophrenia Res* 16:87–110
- Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660–669
- Welham J, McLachlan G, Davies G, McGrath J (2000): Heterogeneity in schizophrenia; mixture modeling of age-at-first-admission, gender and diagnosis. *Acta Psychiatr Scand* 101:312–317
- Woods BT (1998): Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *Am J Psychiatry* 155:1661–1670
- Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET (2000): Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 157:16–25
- Wyatt RJ, Henter ID (1998): The effects of early and sustained intervention on the long-term morbidity of schizophrenia. *J Psychiatr Res* 32:169–177
- Yakovlev PI, Lecours AR (1967): The myelogenetic cycles of regional maturation of the brain. In Minkowski A (ed), *Regional Development of the Brain in Early Life*. Boston, Blackwell Scientific Publications, pp 3–70
- Zwain IH, Yen SS (1999): Neurosteroidogenesis in astrocytes, oligodendrocytes, and neurons of cerebral cortex of rat brain. *Endocrinology* 140:3843–3852